AMENDMENT

Applicants respectfully request entry of the amendments hereinabove, reconsideration of the Final Office Action mailed on June 13, 2005 and allowance of the application.

Applicants herewith submit a Supplemental Disclosure Statement with a new reference.

As a preliminary manner, Applicant(s) request that the Examiner carefully consider the entire text of each reference. It is requested that the references listed on the form PTO-FB-A820 be included in the "References Cited" portion of any patent issuing on this application (M.P.E.P. 1302.12).

Applicants also urge the Examiner to carefully consider all the other references listed in the Information Disclosure Statements of record and those submitted herewith.

EXAMINER'S RESPONSE TO APPLICANTS' ARGUMENTS

The rejection states that Applicants' arguments November 4, 2004 have been fully considered but they are not persuasive with respect to the prior art teaching Ellis et al.

The rejection states that Applicants allege that Ellis et al. do not disclose the use of sildenafil for the treatment of pulmonary hypertension. The rejection states that Ellis et al. specifically teach that inhibitors of cGMP-PDE clearly are used for treating hypertension and pulmonary hypertension, (see page 2). The rejection states that in fact, Ellis et al. refer to EP 463,756, which in turn teaches of pyrazaolopyrimidinone compounds, which clearly render the instant invention obvious. The rejection states that the skilled artisan would have been motivated to use sildenafil and other PDE inhibitors to treat pulmonary hypertension. The rejection states that due to the fact that the very same compound, namely sildenafil, is shown to treat pulmonary hypertension, it would have been inherent that this particular compound sildenafil is also a PDE V inhibitor. The rejection states that the fact that Applicants have further specified a particular isozyme of this enzyme, in this case the type V isozyme of PDE, is an inherent trait or property with the administration of the compounds of Ellis et al. as well as EP 463,756. The rejection states that accordingly, it would have been obvious to the skilled artisan to use the very same PDE inhibitory compounds, such as sildenafil, to treat pulmonary hypertension. The rejection also states that in addition, the skilled artisan is clearly provided with the motivation to use any type V phosphodiesterase inhibitor for the vascular smooth muscle relaxation (vasodilation) in mammals with pulmonary hypertension due to the fact that the very same compound, namely sildenafil, is shown to treat pulmonary hypertension and it would have been inherent that this particular compound of sildenafil is also a PDE V inhibitor. 7.

The rejection also states that second, in response to Applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. The rejection states that but so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See In re McLaughlin,

443 F.2d 1392, 170 USPQ 209 (CCPA 1971). The rejection states that due to the explicit teaching of Ellis et al. the skilled artisan is provided with motivation to use PDE V inhibitors to treat pulmonary hypertension, (see page 2, 2nd full paragraph). The rejection states that clearly, this provides the skilled artisan with motivation to use an inhibitor of PDE V to treat pulmonary hypertension as well as giving the artisan with an expectation of success of treating the ailment of pulmonary hypertension with (text missing from rejection).

The rejection also states that Ellis et al. teach of compounds that are potent inhibitors of cyclic guanosine 3',5'-monophosphate phosphodiesterases (cGMP PDEs). The rejection states that this selective enzyme inhibition lead to elevated cGMP levels which, in turn, provides the basis for many utilities,namely the treatment of hypertension and pulmonary hypertension, (see page 2, 2nd full paragraph). The rejection also states that the skilled artisan would have been motivated to treat patients with an inhibitor of PDE V to treat pulmonary hypertension irrespective of its cause, such as respiratory distress, neonatal hypoxia, post operatively, chronic hypoxia, COPD because Ellis et al. clearly disclose to the artisan that these inhibitors of cGMP PDE are used to treat both hypertension and pulmonary hypertension. Ellis et al. specifically teach of inhibitors of cGMP PDEs with the compounds of formula (I). The rejection also states that in fact, Ellis et al. disclose of "[a] particularly preferred group of compounds of formula (I)" is obtained when R1 is methyl; R2 is n-propyl; R3 is ethyl; R4 is SO2NR9R10; R9 and R10 together withthe nitrogen atom to which they are attached form a 4-N(R12)-piperazinyl group; and R12is methyl, (see page 6, 2nd full paragraph). Ellis et al. also teach of pharmaceuticallyacceptable salts of the compounds of formula (I), (see page 5,1st and 2nd fullparagraphs).

EXAMINER'S 35 USC 103 REJECTION

The rejection states that the rejection of claims 8-10 and 21-112 are rejected under 35 U.S.C. 103(a)as being unpatentable over Ellis et al. of WO 94/28902 possessing a publication date of December 22, 1994, especially for sildenafil and its derivatives is maintained and repeated for both the above-stated and reasons of record. The rejection states that Ellis et al. teach of compounds that are potent inhibitors of cyclic guanosine 3',5'-monophosphate phosphodiesterases (cGMP PDEs). The rejection states that this selective enzyme inhibition lead to elevated cGMP levels which, in turn, provides the basis for many utilities, namely the treatment of hypertension and pulmonary hypertension, (see page 2, 2nd full paragraph). The rejection states that the skilled artisan would have been motivated to treat patients with pulmonary hypertension irrespective of its cause, such as respiratory distress, neonatal hypoxia, post operatively, chronic hypoxia, COPD because Ellis et al. clearly disclose to the artisan application that these inhibitors of cGMP PDE are used to treat both hypertension and pulmonary hypertension. The rejection states that Ellis et al. specifically teach of inhibitors of cGMP PDEs with the compounds of formula (I). The rejection states that in fact, Ellis et al. disclose of "[a] particularly preferred group of compounds of formula (I)" is obtained when R1 is methyl; R2 is n-propyl; R3 is ethyl; R4 is SO2NR9R10; R9 and R10 together with the nitrogen atom to which they are attached form a 4-N(R12)-piperazinyl group; and R12 is methyl, (see page 6, 2nd full paragraph). The rejection states that Ellis et al. also teach of pharmaceutically acceptable salts of the compounds of formula (I), (see page 5,1st and 2nd full paragraphs). The rejection also states that Ellis et al. teach of various modes of administration for these compounds, inter alia, oral and parenteral administration, (see page 10). The rejection states that Ellis et al. further teach of a dosing administration in man ranging from 5 to 75 mg of the compound three times daily, (see page 10, 4th full paragraph). The rejection states that the determination of a dosage having the optimum therapeutic index, modes and methods of administration, for instance inhalation, as well as age of the patient is well within the level of one having ordinary skill in the art, and the artisan would be motivated to determine optimum amounts to get the maximum effect of the drug. The rejection concludes that accordingly, the Ellis et al. reference renders the instantly claimed invention obvious.

WITHDRAWAL OF REJECTIONS

As a preliminary matter Applicants acknowledge the withdrawal of the rejection of Claim 9 under 35 U.S.C. 103(a) as being unpatentable over Takahashi et al.

Applicants also acknowledge the withdrawal of the obviousness-type double patenting rejections over U.S. pat. Nos. 5,250,534 and 5,346,901.

RESPONSE TO EXAMINER'S PRELIMINARY COMMENTS AND 35 USC 103 REJECTION

Applicants traverse the rejection of claims 63-112 (as amended) under 35 U.S.C. 103(a) as being unpatentable over Ellis et al.

Applicants claims are directed to the use of a cGMP PDE **V** inhibitor (i.e., sildenafil) for the treatment of e.g., pulmonary hypertension (underlining and bold added for emphasis).

Initially, Applicants strongly object to the characterization (which appears in at least two places) in the rejection's response to Applicants' previous comments that:

"Due to the fact that the very same compound, namely sildenafil, is shown to treat pulmonary hypertension, it would have been inherent that this particular compound of sildenafil is also a PDE V inhibitor."

"due to the fact that the very same compound, namely sildenafil, is shown to treat pulmonary hypertension"

To reemphasize this point the phrase "Due to the fact that the very same compound, namely sildenafil, is shown to treat pulmonary hypertension" is a statement that it was known that sildenafil per se was known to treat pulmonary hypertension and by implication forms the basis for an anticipation. Applicants strongly submit that their claims are not anticipated by Ellis et al.

This is a mischaracterization of the prior art. Neither EP 0463756, EP-A-0526004, nor Ellis et al. disclose the use of sildenafil for the treatment of pulmonary hypertension. EP 0463756 describes that cGMP PDE inhibitors are useful for treating various disorders; EP 0463756 does not mention the use of any cGMP PDE inhibitors for the treatment of pulmonary hypertension. While EP0526004 does describe that certain cGMP PDE inhibitors are useful for treating pulmonary hypertension EP0526004 does not describe the use of Applicant's claimed compound sildenafil for any indication. Finally, since Ellis et al. refers to both EP 0463756 and EP-A-0526004 in its disclosure regarding pulmonary hypertension Ellis et al. is only disclosing as much as those references disclose -"This selective enzyme inhibition leads to elevated cGMP levels which, in turn, provides the basis for the utilities already disclosed for the said compounds in EP-A-0463756 and EP-A-0526004" (Ellis et al. page 2, second full paragraph). Accordingly, neither EP 0463756, EP-A-0526004, nor Ellis et al. disclose the use of sildenafil for the treatment of pulmonary hypertension. Further, the rejection's

comments regarding inherency "it would have been inherent that this particular compound [of] sildenafil is also a PDE V inhibitor" are not applicable since none of the three references disclose the use of sildenafil for the treatment of pulmonary hypertension. In addition, while the rejection also states the "type V isozyme of PDE is an inherent trait or property with the administration of the compounds of Ellis et al. as well as EP 463,765" Applicants again note that neither Ellis et al. nor EP 463,765 disclose the use of sildenafil for the treatment of pulmonary hypertension.

Applicants submit that their claims are unobvious over Ellis but in an effort to expedite prosecution Applicants have herein canceled claims 8-10 and 21-43 without waiver or prejudice against refilling. Applicants have also amended independent claims 44, 75, 78, 89, 94 and 99 (and consequentially claims depending therefrom) to be independent from the only remaining independent claim 63.

Even assuming arguendo the Examiner's position that the Ellis et al document (WO 94/28902) teaches that the pyrazolo-pyrimidinone compounds disclosed therein are useful in the treatment of hypertension and pulmonary hypertension Applicants submit that their instant claims are unobvious. Alternatively, as Applicants' have stated, EP 0526004 does mention the use of certain cGMP PDE inhibitors for the treatment of both pulmonary hypertension and hypertension (page 2, line 12). However, there is no distinction made in the disclosure between the treatment of hypertension and the treatment of pulmonary hypertension.

For a compound to be useful in the long term treatment of the chronic condition pulmonary hypertension, it should preferably be selective for the pulmonary vascular system compared with the systemic vascular system. This is specifically mentioned in Applicants' application, where it is stated that the decrease in pulmonary vascular system (PVR) must be greater than the decrease in systemic vascular system (SVR) and that preferentially, the compound should lower PVR without any significant decrease in SVR. The human and dog data included in Applicants' specification demonstrate that sildenafil is selective for the pulmonary system compared with the systemic system. Further, any treatment for the chronic condition PHT would preferably have minimal impact on the systemic blood vessels or the patient would suffer adversely from hypotension.

Neither Ellis et al nor EP 0526004 disclose this selectivity or provide a motivation to seek this selectivity. Clearly neither reference provides a reasonable expectation of success that such compounds would have this desired selectivity. In fact EP 0526004

clearly teaches away from Applicants' invention since the disclosure of both PHT and hypertension juxtaposed in the text next to each other implies that the compounds have an equivalent effect on both parts of the vascular system. Clearly one skilled in the art would be motivated to search other scientific avenues for a more selective compound.

Applicants submit that even assuming arguendo that Ellis et al. makes Applicants' invention "obvious to try", "obvious to try" is not the proper standard for patentability. Further, the Examiner has not made out a *prima facie* case of obviousness because, *inter alia* (1) the reference provides no effective motivation or suggestion that sildenafil could or should be tried in the treatment of pulmonary hypertension to selectively reduce pulmonary vascular resistance to a greater extent than systemic vascular resistance in a patient and (2) even allowing, *arguendo*, that any such suggestion or motivation were found in this reference, the reference certainly provides no reasonable expectation of success in the treatment of pulmonary hypertension to selectively reduce pulmonary vascular resistance to a greater extent than systemic vascular resistance in the patient.

The law is emphatic that "obvious to try" is NOT the test of obviousness under 35 U.S.C. §103. American Hospital supply Corp. v. Travenol Laboratories, Inc., 223 USPQ 577, 582 (Fed. Cir. 1984). The Federal Circuit has explained the proper test:

> The consistent criterion for determination of obviousness is whether the prior art would have suggested to one of ordinary skill in the art that this process should be carried out **and would have a reasonable likelihood of success**, viewed in light of the prior art. **Both the suggestion and the expectation of success must be founded in the prior art, not in the applicant's disclosure** (emphasis added).

In re Dow Chemical Co., 5 USPQ.2d 1529, 1531 (Fed. Clir. 1988); Amgen, Inc. V. Chugai Pharmaceutical Co. Ltd. 18 USPQ.2d 1016. 1022-23 (Fed. Cir.), cert. denied, 502 U.S. 856 (1991).

Applicants submit that their claims are unobvious in light of Ellis et al. at least because the proper framework for determining *prima facie* obviousness in this case is to consider all of the relevant art, both that relied on by the Examiner and that cited by Applicants in the Information Disclosure Statements ("IDSs") of record and submitted herewith. Thus, the art as a whole must be considered. *In re Dow Chemical Co.*, 837 F.2d 469 (Fed. Cir. 1988). Further, it is well-settled that "all of the relevant teachings of the cited references must be considered in determining what they fairly teach to one having ordinary skill in the art." *In re Mercier*, 515 F.2d 1161, 1165 (C.C.P.A. 1975); *In*

re Meinhart, 392 F.2d 273, 276 (C.C.P.A. 1968). Essentially, one cannot pick and choose which references to rely on and thus emphasize some and ignore others to reach a conclusion of obviousness.

As applied to Applicants' claims other research papers show the state of research in the field of pulmonary hypertension at or about the time of Applicants' filing date. Applicants submit that the art was one of hypothesis drawing, calls for further research and statements regarding the possibilities of treatment that the research had provided. Specifically, the obviousness rejection must consider such references as Hansanato, et al., American Journal of Physiology, August 1999, vol. 277(2), L225-L232 which was published just prior to the filing of Applicants' application and is evidence of the state of the art at the time.

> "We measured cyclic nucleotide levels in this study and found that long-term treatment with E-4010 (a selective PDE5 inhibitor) increased cGMP levels in lung but not in aortic tissue and did not change camp levels in these tissues. These results suggest that E-4010 is more effective in lung than in aortic tissue and is specific to cGMP, supporting our hypothesis that chronic treatment with a selective PDE5 inhibitor would preferentially decrease cGMP degradation rate and increase [cGMP], in lung tissue due to the predominant distribution of this isoenzyme in the lung. This may be the reason why selective PDE5 inhibitors have pulmonary selectivity. Although we investigated in the present study the chronic effects of E-4010 on the development of hypoxia-induced PH only, one previous study (31[Takahashi et al. described above]) has demonstrated the protective effects of another selective PDE5 inhibitor, E-4021, on the development of right ventricular overload and medial thickening of pulmonary arteries in a different rat model of PH, i.e., monocrotaline-induced PH. In addition, several laboratory and clinical studies (15, 17, 22) have shown that PDE5 inhibitors potentiate the vasodilator effects of inhaled NO. Taken together, these reports suggest the possibility that selective PDE5 inhibitors may be useful in the treatment of PH.
>
> In summary, data of this study have shown that an orally active selective PDE5 inhibitor, E-4010, caused selective pulmonary vasodilation and attenuated the increase in PAP, right ventricular hypertrophy, and pulmonary arterial remodeling induced by chronic hypoxia. These hemodynamic effects of E-4010 were associated with an increase in cGMP levels in lung but not in aortic tissue. These results suggest that E-4010 prevented the development of chronic hypoxia-induced PH, probably through increasing cGMP levels in the pulmonary vascular smooth muscle. We conclude that selective PDE5 inhibitors, including e-4010, may provide a new strategy for the treatment of PH." (underlining added for emphasis)

As described above, throughout the Hansanato et al. document's concluding paragraphs are the caveats that obviate any reasonable likelihood of success. Such qualifiers as "suggest, hypothesis, possibility, may" are continuously used to describe the results of the experiments and predictive value thereof. This is simply not consistent with the standards of obviousness as described in the preceding caselaw descriptions and the requirement for a reasonable likelihood of success.

Further, the paragraph is directed to the possibility of prevention not treatment (note the references to "protective effects", "E-4010 prevented the development of chronic hypoxia-induced PH". Accordingly, there is no disclosure that E-4010 could be used to treat a pre-existing condition.

Even the Takahashi et al. reference cited in a previous rejection is relevant to an understanding of the art as a whole. In that reference, which is more recent than the Ellis et al. reference, research was conducted on whether a PDE5 inhibitor would have functional activity that could possibly predict a viable treatment for pulmonary hypertension.

Applicants submit that the last sentence of the reference clearly summarizes the content of the reference "Our results suggest that the type V phosphodiesterase inhibitor, E4021, administered orally may prove efficacious in the management of patients with pulmonary hypertension and right ventricular overload" (underlining added for emphasis). Applicants submit that even assuming arguendo that there is a suggestion in the art to use Applicants' claimed compounds to treat pulmonary hypertension there is clearly not a reasonable expectation of success since the author admits that further work must be done and that there is only a suggestion that the type V PDE inhibitors may work. This is a classic instance of an invitation to conduct further experimentation. Further, the rejection itself does not address the issue of reasonable expectation of success (it is completely silent as to this necessary element) which is a requirement under the law. Accordingly, the obviousness rejection is clearly not commensurate with the CAFC standards of patentability as described above.

Further, Takahashi et al. in the penultimate paragraph states

> "A limitation of our study was the E4021 was administered before, not after, the development of right ventricular hypertrophy and medial thickening of pulmonary arteries. That is, the therapeutic administration of the drug was started 24 hours after the injection of

> monocrotaline. To gain a further indication of the potential clinical efficacy of E4021, a study should be conducted to assess the effects of E4021 administration beginning 4 weeks after monocrotaline injection, the time at which right ventricular hypertrophy and medial thickening are established. Moreover, it was unclear whether 100 mg/kg/day was an optimal dose for E4021 in terms of protection of the development of righ ventricular hypertrophy and medial thickening of pulmonary arteries. We should examine whether lower doses of E4021 may be similarly effective. Further, adverse effects of E4021 at these doses need to be determined." (underlining added for emphasis)

Thus, Takahashi et al. further acknowledges the limitations of the study.

As described above, in light of the Takahashi et al. more recent research there was only a suggestion that the type V PDE inhibitors may be effective for the treatment of pulmonary hypertension. This is a classic instance of an invitation to conduct further experimentation without the necessary element of a reasonable expectation of success. This reference along with others cannot be ignored in the obviousness analysis, while focusing solely on Ellis et al. Clearly, Takahashi et al., a more recent research paper, reinforces the state of the whole art at the time and also reinforces the tenet that there was not a reasonable expectation of success of a PDE5 inhibitor i.e., sildenafil being an effective treatment for pulmonary hypertension. Further research needed to be performed.

Further neither EP 0463756 nor EP0526004 describe the use of Applicants' claimed compound, sildenafil, to treat pulmonary hypertension. Again, Applicants submit that the art must be taken as a whole and both EP 0463756 and EP0526004 are the basis for the Ellis et al. passage referred to in the rejection. While EP 0463756 describes that cGMP PDE inhibitors are useful for treating various disorders, EP 0463756 does not mention the use of any cGMP PDE inhibitors for the treatment of pulmonary hypertension. Applicants submit that the absence in EP 0463756 of the recitation of pulmonary hypertension (in a lengthy list of other indications) as an indication for cGMP PDE inhibitors strongly implies that cGMP PDE inhibitors are not useful for the treatment of pulmonary hypertension (at a minimum it certainly does not provide a reasonable likelihood of success).

In addition, since sildenafil is included in EP 0463756 and since EP 0463756 implies that sildenafil is not useful for the treatment of pulmonary hypertension,

Applicants' claims directed to the use of sildenafil are not obvious in light of the art when taken as a whole.

Further, while EP0526004 does describe that certain cGMP PDE inhibitors are useful for treating pulmonary hypertension, EP0526004 does not describe the use of Applicant's claimed compound, sildenafil, for any indication.

Accordingly, Applicants submit that when the art is taken as a whole (which it must be) a careful review of Ellis et al.'s statement regarding the utility of the cGMP PDE compounds, along with a review of the references (i.e., EP-A-0463756 and EP-A-0526004) that form a basis for Ellis's statement do not suggest or provide a reasonable likelihood of success that sildenafil would be useful in the treatment of pulmonary hypertension. In the pertinent passage Ellis et al. states "utilities already disclosed for the said compounds in EP-A-0463756 and EP-A-0526004 namely in the treatment of ...". Thus, Ellis et al. is referring to the utilities disclosed in EP-A-0463756 for the compounds of EP-A-0463756 and Ellis et al. is referring to the utilities disclosed in EP-A-0526004 for the compounds disclosed in EP-A-0526004. However, as is stated in the paragraph immediately above, EP 0463756 does not mention the use of any cGMP PDE inhibitors for the treatment of pulmonary hypertension and EP0526004 does not describe the use of any of Applicants' claimed compound, sildenafil, for any indication. While EP-A-0526004 does mention the use of certain cGMP PDE inhibitors for the treatment of pulmonary hypertension it does not suggest that Applicants' claimed compound, sildenafil, would be useful for the treatment of pulmonary hypertension or that there is a reasonable likelihood of success for such treatment. Again, EP 0463756 is silent as to pulmonary hypertension.

Applicants submit that Ellis et al. does not provide a reasonable expectation of success that Applicants' claimed compound, sildenafil, would be useful for the treatment of pulmonary hypertension (to selectively reduce pulmonary vascular resistance to a greater extent than systemic vascular resistance in a patient) since, for example, Ellis et al., does not relate the treatment of pulmonary hypertension to PDE V inhibition. Ellis et al. (merely through the EP0526004 reference) relates the treatment of pulmonary hypertension to generalized cGMP PDE inhibition it does not relate it to PDEV inhibition. Accordingly, when the art is taken as a whole there is no motivation or certainly no reasonable expectation of success that a cGMP PDE V inhibitor would be effective as there are a number of isoforms of cGMP PDE and cGMP PDE V is only one possibility.

Certainly, there is no motivation or expectation of success that a specific PDEV inhibitor sildenafil would be effective.

Restated, Applicants claims are for example, directed to the use of sildenafil (which is a cGMP PDE V inhibitor) for the treatment of pulmonary hypertension to selectively reduce pulmonary vascular resistance to a greater extent than systemic vascular resistance in a patient. Applicants submit that the art must be taken as a whole and both EP 0463756 and EP0526004 are relevant since they are described in the Ellis et al. passage that is referred to in the rejection and they are the basis for that Ellis et al. passage. In the pertinent passage in Ellis et al., EP 0463756 and EP0526004 there is description of the utility of cGMP PDE inhibitors but no mention of a cGMP PDE **V** inhibitor utility (or that any cGMP PDE **V** activity of the recited compounds would be useful for the treatment of pulmonary hypertension). Thus, there is no suggestion that cGMP PDE V inhibitors would be useful for the treatment of pulmonary hypertension or that there is a reasonable likelihood of success for that utility (both being a requirement under current law). There are a number of isoforms of cGMP PDE and cGMP PDE V is only one possibility.

Based on the foregoing, favorable action on claims and 44-112 is requested.

Applicants include herein a Supplemental Information Disclosure Statement.

Authorization is hereby provided to charge the fee for the Supplemental Information Disclosure Statement any additional fees required, or to credit any overpayment to Deposit Account No. 16-1445. Two copies of this paper are enclosed.

Respectfully Submitted,

12/8/05
Date

A. Dean Olson
Reg. No. 31,185
Attorney for Applicants

Pfizer Inc.
Patent Department, MS8260-1611
Eastern Point Road
Groton, Connecticut 06340
(860) 441-4904

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A. Dean Olson
Reg. No. 31,185
Attorney for Applicants

Pfizer Inc.
Patent Department, MS8260-1611
Eastern Point Road
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(860) 441-4904